zinc binding motif (HEXXHXXGXXH) (SEQ ID NO:26) at position 482-492 (numbering according to Kristensen et al., 1994, Biochemistry 33, 1592-8). This motif and a structurally important methionine residue, also thought to reside in PAPP-A at position 556, are strictly conserved within the metzincins, a superfamily of zinc peptidases: astacins, adamalysins (or reprolysins), serralysins and matrixins (matrix metalloproteinases or MMP's)(Bode et al., 1993, FEBS Lett 331, 134-40; Stocker et al., 1995, Protein Sci 4, 823-40).

C1 Cont

IN THE SEQUENCE LISTING

Please substitute the attached Sequence Listing, numbered as pages 1-33 for the Sequence Listing previously submitted.

REMARKS

1. Applicants hereby submit the following:

[ ] a paper copy of a "Sequence Listing", complying with §1.821(c), to be incorporated into the specification as directed above;

[XX] an amendment to the paper copy of the "Sequence Listing" submitted on October 22, 2001, the amendment being in the form of substitute sheets;

[XX] the Sequence Listing in computer readable form, complying with §1.821(e) and §1.824, including, if an amendment to the paper copy is submitted, all previously submitted data with the amendment incorporated therein;

[ ] a substitute computer readable form to replace one found to be damaged or unreadable.

[ ] The computer readable form in this application

no. 09/... is identical with that filed on .... [date sequence was filed] in application no. 09/ , filed [filing date]. In accordance with 37 C.F.R. §1.821(e), please use the [first-filed, last-filed or only, whichever is applicable] computer readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the instant application. A paper copy of the Sequence Listing is [included in the originally-filed specification of the instant application, included in a separately filed preliminary amendment for incorporation into the specification, whichever is applicable].

2. The description has been amended to comply with §1.821(d).

3. The undersigned attorney or agent hereby states as follows:

(a) this submission is not believed to include new matter [§1.821(g)];

(b) the contents of the paper copy (as amended, if applicable) and the computer readable form of the Sequence Listing, are believed to be the same [§1.821(f) and §1.825(b)];

(c) if the paper copy has been amended, the amendment is believed to be supported by the specification and is not believed to include new matter [§1.825(a)]; and

(d) if the computer readable form submitted herewith is a substitute for a form found upon receipt by the PTO to be damaged or unreadable, that the substitute data is believed to be identical to that originally filed [§1.825(d)].

4. Under U.S. rules, each sequence must be classified in <213> as an "Artificial Sequence", a sequence of "Unknown" origin, or a sequence originating in a particular organism, identified by its scientific name.

Neither the rules nor the MPEP clarify the nature of the relationship which must exist between a listed sequence and an organism for that organism to be identified as the origin of the sequence under <213>.

Hence, counsel may choose to identify a listed sequence as associated with a particular organism even though that sequence does not occur in nature by itself in that organism (it may be, e.g., an epitopic fragment of a naturally occurring protein, or a cDNA of a naturally occurring mRNA, or even a substitution mutant of a naturally occurring sequence). Hence, the identification of an organism in <213> should not be construed as an admission that the sequence *per se* occurs in nature in said organism.

Similarly, designation of a sequence as "artificial" should not be construed as a representation that the sequence has no association with any organism. For example, a primer or probe may be designated as "artificial" even though it is necessarily complementary to some target sequence, which may occur in nature. Or an "artificial" sequence may be a substitution mutant of a natural sequence, or a chimera of two or more natural sequences, or a cDNA (i.e., intron-free

sequence) corresponding to an intron-containing gene, or otherwise a fragment of a natural sequence.

The Examiner should be able to judge the relationship of the enumerated sequences to natural sequences by giving full consideration to the specification, the art cited therein, any further art cited in an IDS, and the results of his or her sequence search against a database containing known natural sequences.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made". Since the original paragraph included underlined text, new text has been double underlined.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By: _____
Iver P. Cooper
Registration No. 28,005

IPC:lms
624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\ipc\g-i\hoib\OxviglA\sequence\IPCSeqResponseDisc1.doc

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification:

The subunits of the PAPP-A/proMBP complex can be irreversibly separated by reduction of disulfide bonds and denaturation (Oxvig et al., 1993, J Biol Chem 268, 12243-6). In reducing SDS-PAGE, the PAPP-A subunit has an apparent molecular weight of 200 kDa (Oxvig et al., 1994, Biochim Biophys Acta 1201, 415-23), and its 1547-residue sequence is known from cloned cDNA (Kristensen et al., 1994, Biochemistry 33, 1592-8). PAPP-A is synthesized as a pre-pro-protein (preproPAPP-A), including a 80-residue pre-pro-piece(Haaning et al., 1996, Eur J Biochem 237, 159-63). No proteins with global homology to PAPP-A has been reported in the literature, but PAPP-A contains sequence motifs, including an elongated zinc binding motif (HEXXHXXGXXH) (SEQ ID NO:26) at position 482-492 (numbering according to Kristensen et al., 1994, Biochemistry 33, 1592-8). This motif and a structurally important methionine residue, also thought to reside in PAPP-A at position 556, are strictly conserved within the metzincins, a superfamily of zinc peptidases: astacins, adamalysins (or reprolysins), serralysins and matrixins (matrix metalloproteinases or MMP's)(Bode et al., 1993, FEBS Lett 331, 134-40; Stocker et al., 1995, Protein Sci 4, 823-40).